REMARKS/ARGUMENTS

Request for Examiner Interview

Applicants request the favor of a telephonic interview with the Examiner prior to the issuance of the next Office Action in this application. Applicants' undersigned representative will telephone the Examiner to arrange a convenient time for the interview.

Status of the Claims

Claims 9, 10, 12-17, 19-25, 57 and 58 were rejected. Claims 34-51 have been withdrawn from consideration as being drawn to non-elected inventions. To expedite prosecution, claims 1-8, 11, 18, 26-33, and 52-56 were previously canceled without prejudice or disclaimer. Applicants reserve the right to pursue these claims in a continuation or divisional application or to take other such appropriate action to seek protection of this canceled or withdrawn subject matter.

Claims 16, 17, 24, 25 and 58 have been amended to clarify the invention or to correct minor typographical errors. No new matter has been added by way of the claim amendments. Claims 9, 10, 12-17, 19-25, 34-51, 57 and 58 are now pending in the present application. Reexamination and reconsideration of the claims are respectfully requested in view of the claim amendments and the following remarks. The Examiner's rejections in the Office Action are addressed below in the order set forth therein.

The Objections to the Specification Should Be Withdrawn

The specification has been objected to for failing to provide proper antecedent basis for the use of silicagel matrix as recited in claims 16 and 58 or for the use of the enzymes BpmI and BsgI as recited in claim 25. As noted, Applicants have amended the claims to remove the objectionable matter, and respectfully request that the objection to the specification be withdrawn.

The Objections to the Claims Should Be Withdrawn

Claim 17 has been objected to for containing a typographical error. As noted, Applicants have amended claim 17 in accordance with the Examiner's suggestions, and respectfully request that the objection to the claim be withdrawn.

The Rejection of the Claims Under 35 U.S.C. § 112, Second Paragraph, Should Be Withdrawn

Claim 24 has been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicants regard as the invention. Specifically, the Examiner notes the use of improper Markush language. As noted, Applicants have amended claim 24 in accordance with the Examiner's suggestions, and respectfully request that the objection to the claim be withdrawn.

The Rejection of the Claims Under 35 U.S.C. § 102 Should Be Withdrawn

Claims 17, 19-21 and 23-25 have been rejected under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent Application Publication No. 2003/0113737 (hereinafter "the '737 publication"). This rejection is respectfully traversed.

The '737 publication discloses a method that isolates single-stranded nucleic acid tags for analysis. Such single-stranded nucleic acid tags are isolated by means of one or two restriction endonucleases, one of which preferably nicks double-stranded DNA, wherein the nicked DNA strand will yield a single-stranded nucleic acid tag. Subsequently, the single-stranded nucleic acid tag is captured (*i.e.*, collected) via hybridization and ligation to a double-stranded adapter, which results in "collecting a resulting double-stranded DNA fragment" as required by claim 17.

The Examiner acknowledges on page 15 of the current Office Action that the nicking endonuclease and Type IIS restriction endonuclease described by the '737 publication produces a single-stranded nucleic acid tag rather than a double-stranded nucleic acid tag, as required by step (d) of instant claim 17. However, the Examiner further comments that the open language of claim 17 does not exclude the additional steps disclosed by the '737 publication that would ultimately result in the collection of a double-stranded DNA fragment.

As previously noted, Applicants have amended step (d) of claim 17 to include the language "immediately following step (c)". Applicants' claimed invention now excludes performing additional steps between cleaving the nucleic acid with a restriction enzyme in step (c) and collecting a double-stranded DNA fragment corresponding to the most 5′ end of the RNA in step (d). It is essential to the method of the '737 publication that the additional hybridization and ligation steps be performed following digestion by the nicking endonuclease and Type IIS restriction endonuclease in order to collect a double-stranded DNA fragment. Therefore, Applicants submit that the method of the '737 publication no longer anticipates claims 17, 19-21 and 23-25.

Furthermore, Applicants also maintain that the DNA fragment corresponding to the **most** 5' end cannot be obtained by the method set forth in the '737 publication. The 5' end of the single-stranded tag obtained by the method of the '737 publication is changeable, depending on the recognition site and cleavage site of the nicking endonuclease. The Examples of the cited reference demonstrate this point. See, for example, paragraphs [0791] to [0793], wherein the 5' end of the resulting 10 mer oligonucleotide (5'-CTTTCCTCAC-3'; SEQ ID NO:68) does not correspond to the **most** 5' end of the test RNA molecule (5'-TGAG…), which remains at the 3' end of the adapter (SEQ ID NO:67). In contrast, the method of the Applicants' invention results in a DNA fragment that contains the **most** 5' end of an mRNA molecule.

In light of the foregoing arguments and amendments to the claims, Applicants respectfully request that the rejection to the claims under 35 U.S.C. § 102(e) be withdrawn.

The Rejection of the Claims Under 35 U.S.C. § 103 Should Be Withdrawn

Claim 22 has been rejected under 35 U.S.C. § 103(a) as being unpatentable over the '737 publication in view of U.S. Patent No. 5,484,701 (hereinafter "the '701 patent"). This rejection is respectfully traversed.

The teachings of the '737 publication are described above. The '701 patent teaches that biotinylated primer extension products may be isolated using an antibody-antigen capture system, wherein the antigen digoxigenin is attached to the primer and the primer extension products are captured with a support-immobilized anti-digoxigenin antibody. The Office Action

asserts that it would have been *prima facie* obvious to combine the capture system of the '701 patent with the methods of the '737 publication to achieve the methods of claim 22. Applicants respectfully disagree with this conclusion.

Although the '701 patent discloses the use of a digoxigenin-digoxigenin antibody capture system for isolating primer extension products, it does not teach the collection of a double-stranded DNA fragment corresponding to the most 5' end of the mRNA immediately following cleavage of the nucleic acid with a restriction enzyme, as required by claim 17 from which claims 19-25 depend. Therefore, the '701 patent does not overcome the deficiencies of the '737 publication, and claim 22 cannot be considered *prima facie* obvious in view of the cited references. Accordingly, Applicants respectfully request that the rejection of the claim under 35 U.S.C. § 103(a) be withdrawn.

Claims 9, 10, 12, 14, 16 and 58 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Shibata *et al.* (Biotechniques (2001) 30: 1250-1254) as evidenced by Carninci *et al.* (Genomics (1996) 37: 327-336) in view of U.S. Patent No. 6,383,754 (hereinafter "the '754 patent"). This rejection is respectfully traversed.

The Shibata *et al.* reference teaches the preparation of full-length cDNA libraries by the use of the Cap-Trapper method, and the single-strand linker ligation method (SSLLM) based on double-stranded linkers having a 6-bp protruding end. The '754 patent is directed to the use of Type IIS restriction digestion for cleaving off short tags from randomly fragmented cDNA. The Office Action asserts that it would have been *prima facie* obvious to apply the teachings of the '754 patent to the methods disclosed by the Shibata *et al.* reference to achieve the methods of the present claims. Applicants respectfully disagree with this conclusion.

The Shibata *et al.* reference is explicitly directed towards "constructing the mouse **full-length** cDNA encyclopedia, a comprehensive collection of **full-length** cDNAs (2-4) and their complete sequences." (page 1250, Introduction, emphasis added). The current Office Action states that the Shibata *et al.* reference teaches a method for preparing a DNA fragment corresponding to the most 5' end of an mRNA (page 8), citing the Abstract and Figure 1 of the reference. However, the Abstract of the Shibata *et al.* reference teaches the use of the SSLLM

method to add a double-stranded DNA linker to single-stranded, **full-length** cDNA. The 5' ends are only described in the Abstract as being present within the full-length cDNA insert. Figure 1 of the Shibata *et al.* reference teaches an overview of the preparation of a Cap-Trapper/SSLLM **full-length** cDNA library, describing only **full-length** cDNAs, and not fragments which correspond to the most 5' end of an mRNA. As such, neither the Abstract or Figure 1 teach a method for preparing a DNA fragment corresponding to the most 5' end of an mRNA, as taught by the Applicants' invention. Furthermore, there is no suggestion that the methods of the Shibata *et al.* reference be used to produce DNA fragments corresponding to the most 5' end of an mRNA.

The '754 patent describes a method by which adapters containing a Type IIS restriction site are ligated to cDNA fragments generated by restriction endonucleases. The adapater-ligated cDNA fragments are then cleaved by a restriction endonuclease specific for the Type IIS restriction site and, ultimately, indexed using the Binary Encoded Sequence Tags (BEST) method. However, the '754 patent does not disclose a method for preparing a DNA fragment corresponding to the most 5' end of an mRNA, as taught by the Applicants' invention. As such, the '754 patent does not solve the deficiency of the Shibata *et al.* reference, and the two references cannot be combined to teach the method of the Applicants' invention.

For these reasons, the claims are not *prima facie* obvious in view of the teachings of the '737 publication and '754 patent. Accordingly, Applicants respectfully request that the rejection of the claims under 35 U.S.C. § 103(a) be withdrawn.

Claims 13 and 57 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Shibata *et al.* (Biotechniques (2001) 30: 1250-1254) as evidenced by Carninci *et al.* (Genomics (1996) 37: 327-336) in view of the '754 patent and further in view of Edery *et al.* (Molecular and Cellular Biology (1995) 15(6): 3363-3371) and further in view of Das *et al.* (Physiological Genomics (2001) 6: 57-80). This rejection is respectfully traversed.

The teachings of the Shibata *et al.* reference and the '754 patent are described above. The Edery *et al.* reference teaches the CAPture method for isolating full-length cDNA transcripts using a murine cap-binding protein eIF-4e and an affinity selection procedure. The Das *et al.*

reference is a review article that analyzes and compares a variety of techniques for isolating full-length cDNA. The Office Action asserts that it would have been *prima facie* obvious to one of skill in the art to combine the cited references to achieve the methods of claims 13 and 57. Applicants respectfully disagree with this conclusion.

Neither Edery *et al.* nor Das *et al.* teach or suggest the preparation and collection of DNA fragments corresponding to the most 5' end of mRNAs. As such, they do not solve the deficiencies of the Shibata *et al.* reference and the '754 patent, as described above. Therefore, the methods of claims 13 and 57 are not obvious in view of the cited references. Accordingly, Applicants respectfully request that the rejection to the claims under 35 U.S.C. § 103(a) be withdrawn.

Claim 15 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Shibata *et al.* (Biotechniques (2001) 30: 1250-1254) as evidenced by Carninci *et al.* (Genomics (1996) 37: 327-336) in view of the '754 patent and further in view of U.S. Patent No. 6,022,715 (hereinafter "the '715 patent"). This rejection is respectfully traversed.

The teachings of the Shibata *et al.* reference and the '754 patent are described above. The '715 patent teaches a method for isolating full-length cDNA molecules, wherein the 5' cap structure is modified to contain digoxigenin, which can be selectively captured by an anti-digoxigenin antibody immobilized on a solid support. The Office Action asserts that it would have been *prima facie* obvious to one of skill in the art to combine the cited references to achieve the methods of claim 15. Applicants respectfully disagree with this conclusion.

Although the capture method taught by the '715 patent may be equivalent to the biotin-streptavidin capture method taught by Shibata *et al.*, the '715 patent does not teach or suggest the preparation and collection of DNA fragments corresponding to the most 5' end of mRNAs. As such, it does not solve the deficiencies of the Shibata *et al.* reference and the '754 patent, as previously described. Therefore, the method of claim 22 would not have been *prima facie* obvious in view of the cited references. Accordingly, Applicants respectfully request that the rejection to the claim under 35 U.S.C. § 103(a) be withdrawn.

CONCLUSION

The Examiner is respectfully requested to withdraw the rejections of the claims. In view of the above remarks and claim amendments, it is submitted that this application is now ready for allowance. Early notice to this effect is solicited.

If in the opinion of the Examiner a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefor (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

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